REMARKS

In the Final Action dated October 1, 2010, claims 45-46, 50-54, 60-61, 63-65, 68-71, 87-89, 91 and 133 were pending. Claims 63 and 91 were withdrawn from consideration as directed to non-elected subject matter. Claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89 and 133 were under consideration. Claims 51, 60 and 133 were rejected as allegedly indefinite under 35 U.S.C. §112, second paragraph. Claims 45-46, 50-54, 60, 64-65, 68-71 and 87-89 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Amit et al. (*Developmental Biology* 227: 271-278, 2000) in view of Mummery et al. (*Differentiation* 46: 51-60, 1991), Rohwedel et al. (*Cells Tissues Organs* 165: 190-202, 1999; Abstract), and Rohwedel et al. (*Dev Biol* 164(1): 87-101, 1994).

This Response addresses each of the Examiner's rejections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

35 U.S.C. §112, Second Paragraph Rejection

Claims 51 and 133 were rejected as indefinite because of the phrase "visceral endoderm-like".

Applicant maintains that this term is not indefinite to one skilled in the art in light of the disclosure in the specification.

In the first instance, the specification clearly describes criteria to identify what are visceral endoderm-like properties so as to identify visceral endoderm-like cells. As stated on page 10 and 11, visceral endoderm may be identified by expression of alpha-feto protein (AFP) and cytokeratin (ENDO-A). Hence, "VE-like cells", as used in the present application, can be identified by the marker expression of endoderm proteins. The embryonic cell, which is used to co-culture hES cells in the claimed methods, may be derived from an embryonic cell line, preferably a cell line with characteristics of visceral endoderm (see page 14, line 29). The cell line having characteristics of visceral endoderm is a visceral endoderm-like cell.

The Examiner asserts that "the phrase 'visceral-endoderm-like' can mean digestive system cell or tissue, gland cell or tissue, part of the respiratory cell or tissue". The

Examiner's attention is directed to the fact that the visceral endoderm of the embryo is not generally thought to contribute to adult somatic tissue but to extra-embryonic tissue lineages. The Examiner is confusing visceral endoderm with the definitive endoderm of the embryo that is formed later in embryonic development during gastrulation and does contribute to the formation of the somatic lineages that the Examiner has indicated.

The marker expression profile defined in the specification provides evidence that the END2 mouse cell type has the visceral endoderm-like character, i.e., it exhibits a protein expressing profile of embryonic visceral endoderm. Accordingly, the specification provides a clear description for identifying visceral endoderm-like cells, which a person skilled in the art can rely on to identify the cells.

Furthermore, Applicant submits that the use of this terminology is not uncommon for describing cells in developmental biology. In fact, the USPTO has granted claims to other "cell-like" types. For example, "mesenchymal and fibroblast-like" cells that have been described in U.S. Patent No. 6,642, 048, and are recited in the claims of the '048 patent. For instance claim 23 of US 6,642,048 reads:

> *23. The composition of claim 18, wherein the cells used to condition the medium have been obtained by differentiating a culture of hES cells, and then selecting mesenchymal or fibroblast-like cells from the culture.*

Accordingly, Applicant respectfully submits that the meaning of "visceral endoderm-like" is clear to those skilled in the art; and therefore, claims 51 and 133 are not indefinite.

Claim 60 is also rejected as indefinite because of the recitation, "substantially". While Applicant respectfully disagrees with the Examiner's position for at least the reasons provided in the previous Response, Applicant has amended claim 60 to delete the term "substantially confluent", thereby rendering the rejection moot.

In view of the foregoing, Applicant respectfully submits that the rejection under 35 U.S.C. §112, second paragraph is overcome, and withdrawal thereof is respectfully requested.

35 U.S.C. §103(a) Rejection

Claims 45-46, 50-54, 60, 64-65, 68-71 and 87-89 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Amit et al. (*Developmental Biology* 227: 271-278, 2000) ("Amit") in view of Mummery et al. (*Differentiation* 46: 51-60, 1991) ("Mummery"), Rohwedel et al. (*Cells Tissues Organs* 165: 190-202, 1999 (Abstract)) ("Rohwedel (1999)"), and Rohwedel et al. (*Dev Biol* 164(1): 87-101, 1994) ("Rohwedel (1994)").

Initially, Applicant notes that claim 133 is not included in the rejection. The Examiner is respectfully requested to confirm in the next official communication that claim 133 is unobvious over the cited art.

Applicant respectfully submits that the Examiner's *prima facie* obviousness case is based on an incorrect assumption that there is a "nexus" between EC and ES cells. However, at the priority date of this application, those skilled in the art would not have considered there to be such a nexus. The Examiner has made her own assumption and attempted to bring unrelated conclusions from each of the citations together to draw on the conclusion that the claims are obvious.

In addition, many of Applicant's previous arguments do not appear to have been considered by the Examiner. In particular, the Examiner has not taken into account the differences between EC and ES cells from human or mouse, or the differences between mouse and human cells. Applicant respectfully submits that the Examiner has not considered the claims based on the knowledge and understanding of the skilled addressee at the priority date in respect to these differences.

Applicants respectfully request that the Examiner reconsider in view of the following remarks.

Mummery (1991), Rohwedel (1999) and Rohwedel (1994)

The Examiner's rejection is based on Amit (2000) in view of the citations listed above. Hence the Examiner considers that the deficiencies of Amit should be addressed in the light of the above-referenced citations.

A. Mummery (1991)

The Examiner states: *"Mummery teaches 10^{-9} M Retinoic Acid induces differentiation of P19 EC cells into cardiomyocytes cultured in END-2 feeder cells (p 58, figures 5). Mummery suggests RA is involved in the spontaneous differentiation of P19 EC cells in the END2 system (p59, 1st column 2nd paragraph)."*

Applicant respectfully submits that the Examiner is misinterpreting the data in Mummery (1991) to represent that RA is a component of "the END2 system". The data presented by Mummery (1991) with regard to RA demonstrates the importance of removing endogenous liphophilic molecules (such as RA) from the serum before using the serum experimentally. The serum undergoes charcoal stripping to form DCC-FCS which is then used with the END2 system. The data presented by Mummery (1991) shows that the researchers have gone to great lengths to remove any effect of RA that may be contained in the serum and any involvement in the END2 system.

The data shown in p58, Figure 5, cited by the Examiner, did not use the END2 cell system. The data is presented to demonstrate a concentration dependent effect of P19 cells by RA and standard media with either whole serum or charcoal stripped serum. The experiment shows that by removing lipohilic molecules from the serum through charcoal stripping to form DCC-FCS, mouse P19 EC cells became "exquisitely sensitive" (p58, 1St column, last paragraph) to lower concentrations of RA resulting in differentiation to cardiac and neural lineages at lower concentrations (10^{-10} -10^{-9} M and 10^{-8}M, respectively) while doses normally used (e.g. 10^{-6} M) are now toxic to the P19 lineage. The END2 cell line was not used in these experiments and hanging drops of P19 cells were generated in either the presence or absence of RA in the DF+7.5% DCC-FBS (the charcoal stripped serum).

As outlined in Applicant's previous Response, the charcoal stripping of lipohilic compounds was to remove the confounding effect that endogenous RA in the serum may have on the "END2 system". This is stated in Mummery (1991) in the Results section on p58, 1st column, second to last paragraph:

> *"In non-conditioned medium supplemented with untreated serum rather than DCC-FCS (stripped) serum, approximately 20% of aggregates contained beating muscle, at the earliest 2 weeks after replating (data not shown). This emphasized*

the necessity of removing lipophilic material, including endogenous retinoids, in this type of assay."

Furthermore in the Discussion section of Mummery (1991), the effects of charcoal stripping of the serum to remove endogenous retinoids that may be responsible for the "spontaneous differentiation" of P19 EC cells in whole serum are highlighted in terms of the model END2 system and characterization of its activity by the following statement:

"A model system has been established which will provide a quantitative bioassay for screening during the purification of the END-2 factor; only by culturing and aggregating P19 EC cells in medium supplemented with charcoal stripped serum is "spontaneous" differentiation essentially eliminated".

The experiments conducted by Mummery et al (1991) therefore have gone to great lengths to exclude the potential confounding effect of exogenous RA in the serum by using charcoal stripped FCS for their experiments in the END2 system. Furthermore, RA has not been identified as an active component of the END2 system and the conjecture in the paper is that the active factor may possibly be a novel growth factor protein.

B, Rohwedel (1994/1999)

The Examiner contends that Rohwedel (1994) teaches that P19 EC cells were induced to differentiate into mesoderm-derived cell types by *the FGF-like activity* secreted by feeder END-2 cells. This has not been presented as data in the referenced paper and it is only covered in the Discussion section by reference to the work or personal communication with others, notably Van den Eijnden-van Raaij *et al.* (1991), a reference to a published study previously cited by the Examiner as prior art and withdrawn following Applicant's Response to a rejection based on that reference.

Rohwedel (1994) also states in the Discussion section that, as unpublished data, they also have observed that the *mouse* ES cell line D3 generates mesoderm cell types when exposed to the END2 cell line, in agreement with the observation of Van den Eijnden-van Raaij *et al.* (1991) (p99). Additionally, Rohwedel (1994) notes in the Discussion section that the mouse END2 cell line can induce cardiogenesis in the mouse D3 ES cell line (p99 near end of first paragraph) as has been shown by Van den Eijnden-van Raaij *et al.* (1991) with

mouse P19 EC cells. Importantly, following discussion of the unpublished observations of Van den Eijnden-van Raaij *et al.*, Rohewedel (1994) states: "*However, it is in contrast to the described inhibition of myogenesis in BLC6 derived embryo aggregates*", thereby noting a significant discrepancy of the differentiation inducing effect of the mouse END2 cell line on different mouse ES cell lines. This highlights the unpredictability in this art.

As noted in Applicant's previous Response, the effect of the END2 cell layer in this differentiation system was also noted in the Discussion section of Rohewedel (1994) (p99 column 1): "we found clear differentiation inhibiting-activity for skeletal muscle cell development by visceral endodermal END2 cells...". Skeletal muscle is a mesodermal derivative. There was no inhibitory effect of "authentic" bFGF when added to this system.

Applicant also notes that in the study of Rohewedel (1994), only data from the mouse ES cell line BLC6 was used (see first sentence of Material and Methods) and it was noted that this mouse ES cell line "... in contrast to other ES cell lines... , did not differentiate into cardiac cells" (see first paragraph of the Results section). This furthermore demonstrates that differentiation of this mouse ES cell line (BCL6) was different from other mouse ES cell lines. The effect of the END2 cell layer on cardiogenesis could therefore not be determined by using this mouse ES cell line, BLC6, which differentiated predominately into neuronal and skeletal muscle cells as embryoid body outgrowths with skeletal muscle formation (a mesoderm derivative) being inhibited by END-2 co-culture. Hence, the disclosure of Rohewedel (1994) does not provide adequate teaching for, arguably teaching away from, the use of END-2 cells for mesodermal differentiation. This is a point made in the Introduction section of Rohewedel (1994) (p88 second column, second paragraph) where the authors state that:

> *"Furthermore, we show that a FGF-like activity of visceral endodermal END-2 cells (Van den Eijnden-van Raaij, et al 1991) inhibits skeletal muscle differentiation of ES cell".*

The Examiner also refers to the text in Rohwedel (1994) paper where Shapiro *et al.* (1990) is cited, for allegedly teaching spontaneous myogenic differentiation of a human rahbdomyosarcoma cell line (p101, first col. of Rohwedel (1994)). Given that Rohwedel (1994) teaches that the embryonic feeder END-2 cell line inhibits skeletal muscle

differentiation of the mouse ES cell line BLC6, Applicant presumes that the Shapiro (1990) reference is cited as one example of a source for a human skeletal muscle cell line and to provide supporting evidence for "spontaneous differentiation" to generate skeletal muscle. The cell line described in Shapiro (1990) is obtained from fully differentiated adult tissue that has already formed the skeletal muscle lineage albeit at an earlier stage of differentiation.

Applicant respectfully draws the Examiner's attention to that "embryonic" stem cells are used in the claimed invention, as opposed to "adult" stem cells used in Shapiro (1990).

A rahbdomyosarcoma is "a childhood embryonic tumor of skeletal muscle that rarely demonstrates conclusive evidence of myogenic differentiation characteristic of mature myotubes" (Shapiro 1990, Introduction, p6002, second column). Although this tumorigenic cell type does not form mature, fully differentiated myotubes, it does express early markers of muscle differentiation (e.g. MyoD1) as well as certain membrane proteins found on fetal muscle, "consistent with their developmental arrest at a step after myogenic commitment ...".

Therefore, the "spontaneous myogenic differentiation" of a transformed human cell line derived from a tumor of a cell lineage that is already committed to the formation of the skeletal muscle lineage but is arrested at an immature fetal stage, is not relevant or related to the use of the END2 cell line to induce cardiomyocyte or endothelial formation from pluripotent human ES cells, as presently claimed.

Furthermore, the alleged teaching of "spontaneous differentiation", is by reference to the title of the Shapiro paper and is not itself "taught" by Rohwedel (1994). In fact Rohwedel (1994) notes in the Introduction and Discussion sections the limitations of these committed "muscle cell lines" *in vitro* by stating:

> *"Therefore, muscle cells in culture do not reflect faithfully the in vivo situation regarding the expression of skeletal muscle-specific genes and ionic channels. Moreover, because these cell lines are derived from committed myoblasts, gene activation during the process of commitment into the myogenic lineage cannot be investigated." See* p.88, last paragraph, 1st column.

The "spontaneous differentiation" in the study of Shapiro cited by the Examiner, as allegedly being "taught" by Rohwedel (1994), examined the suppression of myogenic

differentiation of several rhabdomyoblasts (i.e. already committed myoblasts) *in vitro* by establishing several rhabdomyosarcoma cell lines and found that one transformed cell line (Rh28) that emerged during extended passage *in vitro* was able to overcome this suppression of myogenic differentiation and continue on its predisposed differentiation pathway. It is not clear from the Examiner's reference to this publication how this "teaching" could be relevant to the differentiation of pluripotent hES cells that have no commitment to the formation the skeletal muscle lineage and are not trapped in an arrested myoblast state.

As also noted comprehensively in Applicant's previous Responses, there are significant differences between mouse and human ES cells and also considerable differences between ES and EC cells of the same species let alone between species. Applicant reasserts that differentiation conditions that may be effective for mouse ES or EC cells do not translate to conditions that would also work for human ES and EC cells.

FGF-Like Activity

The Examiner also asserts that Rohwedel (1994) *"teaches the embryonic carcinoma cell line P19 isolated from a tertatocarcinoma by ectopic transplantation of a 7.5 day mouse embryo differentiate into mesoderm-derived cell types by the FGF-like activity secreted by feeder END2 cells".*

Applicant respectfully submits that there is currently no evidence that an "FGF-like" activity is a cardiogenic component of the END-2 co-culture system, and this is pure conjecture. The only suggestion in Rohwedel (1994) that an FGF-like activity may exist is by reference to Van den Eijnden Raaij as a personal communication where Rohwedel (1994) notes the preliminary nature of this conjecture by stating in the Discussion section (paragraph 1, first column, p99) that

> *"Up to now, the active principle of END-2 cells is not purified but preliminary data give evidence for a FGF-like activity (Eijnden-van Raaij, personal communication)."*

The fact that an FGF (or any other peptide growth factor) has not subsequently been identified that is produced by the END2 cell line (let alone defined as FGF-like) that can be isolated and shown to have a similar cardiogenic effect as the END-2 cell line is described

in Mummery (1991), a paper that also includes Van den Eijnden-van Raaij as a co-author and is cited by the Examiner. The following statement (p.59, first paragraph) from that paper is relevant to the conjecture of an FGF-like activity:

> *"A number of well-established growth factors produced by EC cells or their differentiated derivatives... such as Transforming Growth Factor-β (TGFβ), Platelet Derived Growth Factor (PDGF) and Fibroblast Growth factor (FGF), are without effect on P19 aggregates even in charcoal stripped serum, so that it is possible that the "END-2" factor has not been described previously."*

Furthermore, the discussion in this paper goes on to comment on "[s]tudies are currently *in progress to characterize and purify it..."*

It appears that the Examiner is trying to use the Rohwedel (1994) paper as an alternative means of referring back to the teaching of the Van den Eijenden-van Raaij (1991) paper in support of an obviousness rejection. By using a paper (and personnel communication) referenced by Rohwedel (1994), the Examiner appears to attempt to resurrect a publication (Van den Eijenden-van Raaij (1991)), which was the basis of a previous obviousness rejection that has been overcome and withdrawn.

Retinoic Acid

The Examiner further asserts that Rohwedel (1999) teaches *"modulation of ES cell differentiation in vitro by RA depends on the concentration and developmental stage of the application which is comparable to its stage-dependent influence on embryonic development in vivo".* Applicant has already provided evidence that human ES cells do not behave in a similar manner to *mouse* ES cells which are the cell type described by Rohwedel (1999). Applicant is not clear as to the insistence of the Examiner in relying on RA-based differentiation treatment of mouse ES cells, as the claimed methods do not involve any use of RA to effect the differentiation of human ES cells towards mesodermal lineages.

The Examiner also states that Rohwedel (1999) teaches *inhibition* of cardiomyocyte bodies but *induction* with 10^{-9} M RA after day five. Applicant has already demonstrated to the Examiner in the previous Response that RA is toxic to hES cells under similar differentiation conditions (see supplemental data to Xu *et al* (2002) and Exhibit 2 (not

Exhibit A as identified incorrectly by the Examiner)). Hence the disclosure of Rohwedel (1999) in respect to RA would not be relevant to the culture and differentiation of human ES cells as presently claimed.

The Examiner further states that Rohwedel (1999) teaches a "nexus" between ES and EC cells. The study described in Rohwedel (1999) is directed to mouse embryogenesis, and both cell types (ES and EC) described in Rohwedel (1999) are derived from mouse. Any nexus between mouse ES and EC cells, which the Examiner attempts to establish, is negated by the disclosure of Rohwedel (1994), which shows a mouse ES cell line (BCL6) that does not show the same differentiation potential or responds in the same manner as either, another mouse ES cell line (D3), or a mouse EC cell line (P19). Under the same differentiation conditions, the mouse ES cell line BCL6 actually shows the opposite response, i.e. inhibition of mesodermal differentiation following an END2 treatment.

Furthermore, the Amit (2000) reference also states in the introduction (p27, second column)

> *"Although the mouse is the mainstay of experimental mammalian developmental biology, there are significant differences between early mouse and human development."*

It is also stated in the Introduction section of Amit (2000): "Human ES cells should provide important new insights into the differentiation and function of tissues that differ significantly between mouse and human."

In light of the foregoing, it is unclear how the Examiner could draw a conclusion on the effect of RA on human ES cells, solely based on the effects of RA on mouse ES and EC cells, despite the differences between mouse and human cells as well as between different mouse cells, as well recognized by those skilled in the art.

Combining Mummery (1991) and Rohwedel (1994/1999) with Amit (2000)

The Examiner subsequently states that Mummery (1991) and Rohwedel (1994/1999) teach the "nexus" of END-2 FGF-like activity and RA for the induction of mouse ES cells. As discussed above, no FGF-like activity has been isolated from the END-2 cell line. The effects of RA were also investigated separately from the END-2 cell line to

remove the potentially confounding effect of RA that may be present in the serum and is a well known dosage-dependent inducer of mesoderm in mouse P19 EC cells, while the effect of RA on human ES cells has already been noted as being toxic in the study by Xu *et al* (2002) (provided with Applicant's previous Response).

The Examiner also states subsequently that given the presumed teaching of Mummery (1991) and Rohwedel (1994/1999) of an FGF-like activity and RA for the induction of mouse ES cells, the use of END-2 feeder cells would be apparent from Amit (2000) "that human ES cells cultured on MEFs bFGF maintains the human ES cells in an undifferentiated state thus FGF-like activity secreted by feeder END-2 cells would induce cardiomyocyte differentiation as noted by Rohwedel (1994)". (Emphasis added.)

Besides the obvious contradiction by the Examiner in the use of a feeder cell layer and an FGF-like activity to both prevent differentiation and to induce differentiation of human ES cells, no FGF-like activity has been isolated and identified in the END-2 feeder cell layer. As discussed above, the suggestion in Rohwedel (1994) that an FGF-like activity may exist is a pure conjecture.

The use of the END-2 cell line by Rohwedel (1994) and the particular mouse ES cell line used in that study, also taught that mesoderm formation was inhibited by the END-2 cell line. In addition, Amit (2000) also teaches away for the use of a feeder cell layer and any FGF-like activity for the differentiation of human ES cells, as the feeder layer and bFGF used in Amit were to maintain the human ES cells in a pluripotent undifferentiated state during continuous cell culture. Hence, these citations should not be combined.

The Examiner further states that "[o]ne of skill in the art would have used the END-2 feeder cells for human ES cell differentiation particularly in view of the teaching by Amit that identifying the factors that the fibroblast produce that promote human ES cell renewal will be critical to large-scale growth, because feeder cell layers are labor intensive to prepare and because variation between batches of fibroblast can introduce undesirable variation and complexity to experiments (p277)."

The Examiner also states that "Amit teaches that serum is a complex mixture that can contain compounds both beneficial and detrimental to human ES cell culture (p276, 1st

column). Different batches of serum vary widely in their ability to support vigorous undifferentiated proliferation of human ES cells." (Emphasis added.)

The fact that serum is a complex mixture is exemplified by Mummery (1991) who went to great lengths to remove lipophilic molecules (including RA) from serum (FCS) by charcoal stripping. The fact that Amit (2000) used an embryonic feeder layer (MEF5) and batch qualified serum for the "undifferentiated proliferation" of human ES cells is clearly irrelevant to the use of embryonic cell layers and serum containing media for the differentiation of human ES.

Summary

1) There is no FGF-like activity that has been isolated and identified in the END-2 culture system and its existence is pure conjecture.

2) The studies with RA in the Mummery (1991) paper did not involve the use of the END-2 cell line. RA has not been shown to be an active component of the END2 system.

3) There is no direct teaching of the use of RA or an FGF-like activity in the Rohwedel (1994) paper or any other prior art.

4) There is no nexus between RA or an FGF-like activity and the END2 system.

5) Rohwedel (1994) demonstrates that a mouse ES cell line (BLC6) is inhibited from forming mesoderm when exposed to the END-2 cell line, in contrast to the claimed invention, which also highlights the differing response of mouse ES and EC cells.

6) Amit (1990) uses embryonic feeders (MEF5) and FGF-like activity (bFGF) to maintain hES cells in an undifferentiated state. The teaching of Amit is irrelevant to, and arguably teaches away from, the use of an embryonic cell layer for directed differentiation.

The Examiner appears to be asserting that an FGF-like activity and RA, both allegedly produced by an embryonic cell line, are responsible for the bioactivity of the END-2 cell line and that due to allegedly known effects of these factors on mouse ES and EC cells (i.e. mesoderm inducers), the effects of these factors on human ES cell are predictable.

As discussed above and submitted in Applicant's previous Response, there was no demonstrated or published evidence that an FGF-like activity or RA has anything to do with

the cardiogenic activity of the END-2 cell line or another embryonic cell line that induces differentiation of hES cells, at the time of the present invention.

As noted above, the experimental evidence available at that time would indicate that proteins of the FGF family or small lipophilic molecule are *not* components of the cardiogenic activity of the END-2 system.

Further, the Examiner continues to ignore the fact that there are known differences between the EC and ES cells, and between the mouse and human cells, which are well recognized in the art, including Amit (2000) (page 271, 2nd column, referenced *supra*). Thus, the effect of RA on hES cells, if any, would not be predictable from the study of this compound on mouse ES and EC cells, as evidenced the study of Xu *et al.* (2002) (discussed above and in the Response to the previous office action).

Applicant respectfully submits that in the recent Supreme Court's decision, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Court states that with respect to a combination of prior art references, an invention is not obvious if the combination of old elements is not a predictable use of these elements according to their established functions giving predictable results. See, e.g., *Id.*, at 13. In the present case, the Examiner has not met her burden to establish that the combination of the elements disclosed separately by the respective references is a *predictable* event according to their established functions giving *predictable* results, especially in light of the evidence of unpredictability in the art as discussed hereinabove.

In view of the foregoing, Applicant respectfully submits that the claimed invention is not obvious over the cited combination of art. Withdrawal of the obviousness rejection is respectfully requested.

Conclusion

It is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser, P.C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
Telephone: 516-742-4343
XZ:eb